Remarks

Claims 1-3, 5-11 and 19-27 are pending. Claim 2 has been amended. Claim 4 has been canceled.

Rejection Under 35 U.S.C. § 112, first paragraph (written description)

Claims 1-11 and 19-27 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention and indefiniteness. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 1 recites:

A method to decrease angiogenesis comprising

administering to a site in an individual in need of treatment thereof for an established disorder requiring angiogenesis an effective amount of a purified chondroitinase to decrease angiogenesis at the site,

wherein the decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of capillary-like structures.

The language is issue is "an established disorder requiring angiogenesis". Disorders requiring angiogenesis are listed on pages 10-11 of the specification. Metastasis of an established tumor is described on page 1, line 22 to page 2, line 3 as requiring angiogenesis. A tumor larger than 2-3 mm^3 requires angiogenesis to supply nutrients to the tumor. Thus once a tumor is palpable or large enough to break through the basal lamina and enter the bloodstream, it

is established in the host. On page 10, line 8 it states that chondroitinases are used "to inhibit formation, growth and/or metastasis of tumors." In order to inhibit growth and/or metastasis of a tumor, the tumor first needs to be established. If a tumor is not established, it can not grow of metastasize. Similarly on page 6 lines 11-14 the actions of Chondroitinase AC and chondroitinase B regulate tumor growth and metastasis by decreasing endothelial cell proliferation and capillary formation and thereby reducing tumor cell access to the bloodstream.

Example 6 on page 17 of the specification describes the inhibition of growth of capillary-like structures in an *in vitro* angiogenesis assay after treatment with chondroitinase AC. Example 9 on page 19 describes the treatment of a mouse with cancer, an *established* disorder characterized by palpable tumors, with chondroitinase AC. The examples of the specification demonstrate that at the time of filing, the Applicants were in possession of the claimed invention.

In summary, there is clear support for the reference to an established disorder requiring angiogenesis in the specification. However, to the extent the examiner is objecting to the term "established", this word has been deleted from the claims.

Claim 2 has been amended merely to reorganize the claimed subject matter for clarity. The Markush group format is proper and defines the enzymes as being expressed recombinantly from bacteria.

The term "enzymes expressed from recombinant nucleotide sequences in bacteria" is not indefinite. One of skill in the art would understand that the enzymes listed in the Markush group of claim 2 would be expressed recombinantly from bacterial cells. "Recombinant nucleotide sequences" is an art-recognized term and techniques to express the enzymes are routine in the

art. The methods are referenced on page 12, lines 24-26 of the specification to Gu *et al. Biochem J* 312:569-577 (1995).

Rejection Under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-11 and 19-27 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The test of enablement is whether one of ordinary skill in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 199 U.S.P.Q. 659 (C.C.P.A. 1976). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 13321, 1332 (Fed. Cir. 1991); *Spectra-Physics, Inc. v. Coherent*, Inc., 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987).

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the

breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The claims are directed to a method for decreasing angiogenesis in an established disorder requiring angiogenesis. While the disorders listed on page 10 and 11 of the specification may be distantly related because of other symptoms, the mechanism that applicants address, angiogenesis, is the same regardless of the disorder. Angiogenesis involves endothelial cell proliferation, migration and tubule formation with associated changes in the extra-cellular matrix, allowing subsequent new vessel growth toward the tumor.

The Examples clearly demonstrate that applicants are able to inhibit the mechanism of angiogenesis, not just angiogenesis associated with tumor cell proliferation. Example 5 demonstrates inhibition of endothelial cell proliferation in a dose dependent manner following treatment with chondroitinase AC. Endothelial cells make up new blood vessels and proliferation is required for angiogenesis. Example 6 on page 17 demonstrates the inhibition of growth of capillary-like structures in an *in vitro* angiogenesis assay after treatment with chondroitinase AC. Growth of new capillaries is required for angiogenesis. Example 8 on page 18 demonstrates that chondroitinase AC treatment can increase apoptosis in vascular endothelial cells, further showing that the claimed method is generally applicable. Inducing programmed

cell death in vascular endothelial cells can decrease established blood vessels and prevent new ones from forming. Example 9 on page 19 describes treatment of C57BL mice with *established* palpable tumors by administration of 55 IU of Chondroitinase AC. Tumor size significantly decreased in the treated mice compared to untreated controls.

In summary, the applicants have clearly demonstraed that the enzymes can be used to inhibit angiogenesis generally, not just tumor growth. The methods of administration are known and described on page 12. An effective dosage is described on page 12, lines 18-22 of the specification.

Rejection Under 35 U.S.C. § 102

Claims 1, 2, 4-6 and 8 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,696,816 to Brown ("Brown"). Claims 1, 2, 4, 5, 9, 10, and 27 were rejected under 35 U.S.C. § 102(b) as being anticipated by Takeuchi Br J Cancer 26, 115 (1972) ("Takeuchi"). Claims 1-5, 8-11, 24, 25, and 27 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 96/01648 to Ibex Technologies, Inc ("Ibex"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Claimed Subject Matter

The claims are drawn to a method to prevent angiogenesis to treat disorders associated with angiogenesis.

The Prior Art

Brown

Brown relates to a method to degrade cartilaginous tissue by administering chondroitinase and collagenase. (see col 4, lines 25-27 and 42-25) Cartilaginous tissue is avascular. Degradation of cartilage has nothing whatsoever to do with inhibition of angiogenesis. Therefore Brown does not disclose the claimed subject matter.

The section the examiner has referred to is incompletely excerpted. The full quote, which makes it quite clear that the disclosure does not refer to treatment of tumors by inhibition of angiogenesis but by degradation of cartilage, reads as follows:

"The enzyme's pharmaceutical use is not limited to nucleus pulposus, but should find application in the treatment of ganglia, arthroscopy of joints, certain eye conditions, tumors and ***other unwanted cartlage tissue***." Col. 4, lines 42-45.

Takeuchi

As the examiner will understand for the foregoing discussion, applicants have clearly demonstrated that they administer enzyme to inhibit endothelial cell proliferation and thereby inhibit angiogenesis.

Endothelial cells are not tumor cells.

Applicants have demonstrated that tumor cell growth can be inhibited by inhibiting angiogenesis – i.e., by decreasing the blood supply to the tumors, by inhibiting endothelial cell proliferation.

Takeuchi does not inhibit endothelial cell proliferation. Takeuchi inhibits tumor cell proliferation by direct administration of enzyme to the tumor cells, prior to or at the time of implantation of the tumors.

This is not the same as inhibiting angiogenesis as claimed. Therefore the claims are novel over Takeuchi.

Takeuchi also does not make obvious the use of enzyme to inhibit angiogenesis since Taeuchi states that the enzymes are acting directly on the tumor cells (see abstract). In contrast, as applicants demonstrate by their examples, they add enzyme to act on endothelial cells – inhibiting their proliferation.

Takeuchi states on page 119, 1st column that "from these results it is conceivable that chondroitin sulphate serves as a growth supporter which protects the surface of tumour cells and promotes the physiological surface function of the cells." There is simply no teaching that one skilled in the art could administer enzyme in an amount effective to inhibit angiogenesis.

Ibex

Ibex describes a method to modulate wound healing using proteoglycan degrading enzymes. A wound is not normally considered a disorder. A wound is an acute trauma.

Moreover, the mechanism of action described by Ibex is different. As described in the summary on page 9, at line 22 to page 10, line 30. The preferred enzyme is heparinase 3. The enzyme releases growth factors to cause cell proliferation, not inhibition of cell proliferation, as claimed.

The examiner has referred to page 5 of Ibex. The reference on page 5 is not to any method of treatment, but describes the ordinary course of events in wound healing, including migration of keratinocytes and epidermal cells in response to chemoattractant and angiogenic signals.

In summary, Ibex does not describe a method of inhibiting angiogenesis.

Ibex actually teaches away from the claimed method because one of skill in the art would not expect administration of chondroitinase to decrease angiogenesis in view of the disclosure of Ibex.

Rejection Under 35 U.S.C. § 103

Claims 1-11 and 19-27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sasisehkaran, in view of Takeuchi and Brown. Claims 1-11 and 19-27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Takeuchi, in view of Ibex and Brown. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Sasisehkaran, in view of Takeuchi and Brown

The claims are directed to a method for decreasing angiogenesis by administering a chondroitinase. Sasisehkaran discloses a method to inhibit angiogenesis by administering an effective amount of heparinase. Heparinases have been shown to decrease cellular proliferation during wound healing and decrease angiogenesis (see Ibex above).

Ibex demonstrates that heparinases and chondroitinases not only have different mechanisms of action but act antagonistically (Ibex Figures 3 and 5, and accompanying discussion).

Brown states that one can use enzymes to degrade cartilage.

In combination, one of skill in the art would be led to use heparinases to enhance wound healing by increasing proliferation of cells (Ibex), or to degrade cartilage (Brown) or inhibit tumor cell proliferation (Takeuchi). There is no teaching to combine. There is nothing that would lead one to have a reasonable expectation of success by combining and modifying the references as applicants have done. Therefore the combination does not make obvious the claimed methods.

Takeuchi, in view of Ibex and Brown

Takeuchi describes inhibition of tumor cell proliferation. Ibex describes using a glycosaminoglycanase, preferably heparinase, to promote cellular proliferation and angiogenesis. Brown describes degrading cartilage.

There is no motivation to combine these references.

There is nothing leading one to modify the references to arrive at the claimed methods.

There is nothing that would lead one to have a reasonable expectation of success using the claimed method to inhibit angiogenesis. Therefore, claims 1-11 and 19-27 are not obvious over Taeuchi in view of Ibex and Brown alone or in combination.

Allowance of claims 1-11 and 19-27 is respectfully solicited.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: October 17, 2003

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)

Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, Notice of Appeal, Petition for Extension of Time under 37 CFR 1.136(a), and any documents referred to as attached therein are being facsimile transmitted on this date, October 17, 2003, to the Commissioner for Patents, U.S. Patent and Trademark Office, Alexandria, VA 22313-1450.

Patrea Pabst

Date: October 17, 2003

595770_v1